Remarks

Status of the Claims and Support for the Amendments to the Claims

By the foregoing amendments, claims 26-35, 38-50, 53-61, 63-68 and 70-72 have been canceled without prejudice or disclaimer. Claims 1, 7 and 8 are sought to be amended in order to correct inadvertent typographical errors and to update the dependency of these claims. New claims 75 and 76 are also sought to be added. Support for new claims 75 and 76 can be found throughout the specification, particularly throughout Example 3. Therefore, these amendments introduce no new matter. Upon entry of the foregoing amendments, claims 1-4, 7, 8, 12, 69 and 73-76 are pending in the application, with claims 1 and 73 being the independent claims.

Summary of the Office Action

In the Office Action dated July 28, 2005, the Examiner has made three rejections of the claims. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Priority Date of the Present Application

In the Office Action at page 2, section 3, the Examiner contends that the filing date of the present application is deemed to be filing date of PCT Application No. 2000/04392, filed February 22, 2000, as the priority application, Provisional Application No. 60/121,133, filed February 22, 1999, allegedly does not support the subject matter of the present claims. Applicants respectfully disagree with the Examiner and submit that the present invention is supported by the disclosure of Provisional Application No. 60/121,133. Hence, Applicants

respectfully request reconsideration of the priority date determination of the present application.

The Rejections Under 35 U.S.C. § 112, Second paragraph

In the Office Action at page 2, section 5, the Examiner has rejected claims 7 and 8 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

By the foregoing amendments, claims 7 and 8 have been amended such that claims depend directly from claim 1, and the phrase "antibody or" has been removed from claim 8. Hence, the rejection under 35 U.S.C. § 112, second paragraph has been overcome. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection Under 35 U.S.C. § 103(a) Over Yu, In View of Wang, Nilsson and Martin

In the Office Action at pages 3-5, section 7, the Examiner has rejected claims 1-3, 7, 12, 73 and 74 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Yu *et al.*, *Oncogene 11*:1383-1388 (1995) (hereinafter "Yu"), in view of Wang *et al.*, *Bioconjugate Chemistry 8*:878-884 (1997) (hereinafter "Wang"), Nilsson *et al.*, *Current Opinion in Structural Biology 2*:569-575 (1992) (hereinafter "Nilsson") and Martin *et al.*, *J. Biol. Chem. 257*:286-288 (1982) (hereinafter "Martin"). Applicants respectfully traverse this rejection.

The Examiner contends that Yu discloses cationic liposome-mediated E1A gene transfer, and the use of anti-p185 antibodies to construct immunoliposomes. The Examiner also contends that Yu discloses using a DNA:liposome ratio of 1:13, which allegedly falls

within the range recited in present claim1. The Examiner states that Yu does not disclose the use of an antibody fragment, including scFv, nor the ratio of incorporation of antibodies into the liposomes. The Examiner also states that Yu does not disclose direct conjugation between an antibody fragment and a liposome via a sulfur atom that was part of a sulfhydryl group at a carboxy terminus of the scFv. The Examiner relies on the disclosures of Wang, Nilsson and Martin to cure these deficiencies.

The Examiner contends that Wang discloses generation of an scFv with a carboxy terminal cysteine for the purpose of covalently linking the scFv-cys to a toxin through a disulfide bond. The Examiner further states that Wang discloses the advantages of using scFvs rather than intact antibodies.

The Examiner states that Nilsson discloses targeting of drugs to a specific cell types using monoclonal antibodies, and that scFv fragments have simplified the production of recombinant antibody fragments.

The Examiner finally contends that Martin discloses coupling of Fab' fragments to liposomes via a sulfur atom on the Fab' using MPB. The Examiner states that Martin discloses that it is possible to link any thiol-containing protein ligand to MPB-PE containing liposomes. The Examiner also contends that Martin discloses ratios of Fab' fragments:liposomes that fall within the range required by the present claims.

Based upon these alleged disclosures, the Examiner concludes that it would have been obvious for one of ordinary skill in the art at the time of the filing of the present application to have made an scFv antibody such as disclosed in Nilsson, with a carboxy terminal cysteine residue such as disclosed in Wang, having the anti-P185 antibody specificity as disclosed in Yu, and to have coupled it to the cationic liposome disclosed in

Yu using the method disclosed in Martin, to produce the immunoliposome of the presently claimed invention. The Examiner contends that the motivation to combine these four references is based on the fact that the ordinarily skilled artisan would have recognized the advantages of scFvs as targeting moieties, and therefore would have substituted them for the Fab' fragments disclosed in Martin using the methods of Wang. Applicants respectfully disagree with the Examiner's contentions and the conclusion that the presently claimed invention is rendered obvious by this combination of references.

Applicants respectfully submit that Yu does not disclose an antibody-fragment-targeted cationic immunoliposome complex, wherein the antibody fragment is directly conjugated to the cationic liposome, nor the use of a sulfur atom which was part of a sulfhydryl group for such conjugation. In fact, Yu does not disclose an antibody fragment-targeted immunoliposome prepared by any method. Yu simply mentions in passing that liposomes could be targeted to the HER-2/*neu*-encoded p185 receptor. However, Yu provides no disclosure of the methods, ratios of lipid to protein, conditions, or other requirements for creating such immunoliposomes. In fact, Yu admits that such targeted liposomes could only be prepared once a ligand for the HER-2/*neu*-encoded p185 receptor *becomes available* (*see* Yu at page 1387, column 1, last line of the first full paragraph).

Applicants respectfully submit that, at most, Yu provides a disclosure of a wish or a dream of preparing cationic immunoliposomes. However, Yu clearly does not disclose or enable any method for preparing such immunoliposomes, much less the immunoliposomes of the present invention. Applicants respectfully submit that these deficiencies are not cured by the disclosures of Wang, Nilsson and Martin, alone, or in combination.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). The Examiner has not met this burden.

Wang only discloses linking antibody fragments to toxins. Wang does not disclose in any way that scFvs could be, or should be, linked to cationic liposomes. Hence, Wang provides no motivation to the ordinarily skilled artisan to construct the nucleic acid-cationic immunoliposome complex of present independent claim 73, where antibody fragments are directly conjugated to a liposome.

Furthermore, with regard to present independent claim 1, Wang does not disclose that the ratio of protein:lipid is in the range of 1:5 to 1:40, as recited in this claim. Wang does not even mention the use of liposomes, much less the use of a ratio of protein:lipid that would render obvious the ranges required in present claim 1.

The molar ratio of scFv to toxin disclosed in Wang is 1:1 to 1:2 (*see* Wang at page 879, column 2, second paragraph). Present claim 1 requires a wt:wt ratio of scFv to liposome of 1:5 to 1:40. Utilizing a molecular weight of 28kD for an exemplary scFv (*see*, Molecular Cloning: a Laboratory Manual, 3rd edition, by Sambrook and Russell, Cold Spring Harbor Press, 2001) and a molecular weight of an exemplary liposome composition of the present invention of approximately 744 g/mol (molecular weight of DOPE).

1 μg of scFv is equivalent to approximately 0.036 nmol of protein,

therefore, 1 μg is equivalent to 36 μmol of protein; and

1 μg of liposome is equivalent to approximately 1.4 nmol of lipid,

therefore, 5 μg of liposome is equivalent to 7 nmol of lipid,

therefore, 40 μg of liposome is equivalent to 56 nmol of lipid.

Therefore, the wt:wt (*e.g*, μg) ratios of scFv:liposome in present claim 1 of:

1 μg:5μg to 1 μg:40 μg,

correspond to a molar ratio of:

0.036 nmol protein:7 nmol lipid to 0.036 nmol protein:56 nmol lipid,

which reduces to a molar ratio of:

1:194.4 to 1:1555.6 (scFv (protein):liposome (lipid)).

Thus, the molar ratios recited in present claim 1 are clearly different from the 1:1 to 1:2 molar ratio of protein to toxin disclosed in Wang. The difference is significant, and extensive experimentation would be required by the ordinarily skilled artisan, with no guidance provided in Wang, to reach the ratios recited in present claim 1. Applicants respectfully submit, as evidenced by the dramatic differences in ratios of protein to lipid noted above, that there is a significant difference between linking an antibody fragment to a protein, such as a toxin, and to a liposome, and the fact that the former could be done does not lead a person of ordinary skill in the art to expect that the latter also could be accomplished. Applicants respectfully submit that Wang provides no motivation or suggestion to directly link an antibody fragment to a liposome, and the ordinarily skilled

artisan would not have had a reasonable expectation of success to accomplish such a combination, as further evidenced by the dramatic disparity in the ratios of protein required.

Nilsson also does not disclose conjugation of antibody fragments to cationic liposomes, and in fact, Nilsson does not disclose any methods for preparing cationic immunoliposomes. Nilsson is instead limited to the production of fusion proteins. There is no discussion in Nilsson of using an scFv with a liposome, or of using an scFv for targeted delivery and there is also no disclosure of conjugating an scFv to a liposome through a sulfur atom which is part of a cysteine residue. Thus, Applicants respectfully submit that Nilsson provides no motivation to prepare a nucleic acid-cationic immunoliposome of the present invention which requires directly conjugating an scFv to a liposome, and the Examiner has not provided any indication that the ordinarily skilled artisan would have had a reasonable expectation of success of preparing such an immunoliposome based upon the disclosure of Nilsson.

With regard to Martin, Applicants respectfully submit that the disclosure of this reference is limited to coupling of Fab' fragments, not scFv fragments, to liposomes. Martin makes no suggestion of preparing scFv-liposome complexes. Applicants respectfully submit that an Fab' is quite different from an scFv. The two fragments have different structures and sizes and different behaviors and uses. Furthermore, Martin does not give any guidance as to what ratio one would use with an scFv rather than an Fab'. This lack of guidance is significant, especially because of the difference in size of the two types of fragments (Fab' are about 55-60 kDa; scFv are approximately 24-28 kDa). The ordinarily skilled artisan, guided only by the disclosure of Martin, could not expected to be able to simply replace one type of antibody fragment with the other. Hence, the Examiner has not provided sufficient

motivation, or a reasonable expectation of success, to utilize scFvs in the methods disclosed in Martin which are directed to coupling of Fab' fragments.

The Examiner contends that Martin discloses coupling of antibody fragments to liposomes at a ratio of 250 μg Fab' fragments to 1-2 μmol of liposome, a wt:wt ratio of about 1:24 - 1:48, or 1.4 μmol/ml lipid to Fab' at 0.5-4.0 mg/ml, a wt:wt ratio of about 1:14 - 1:2 protein to lipid. Applicants respectfully disagree with the Examiner's contentions, and submit that the ratios disclosed in Martin are, in fact, very different, as set forth below:

From Martin at page 286, column 2, 3rd full paragraph, the ratios of Fab' protein fragment to lipid used are:

0.5 to 4 mg Fab' fragments to 1-2 μmol phospholipid

Based upon the micromolar ratios of the three components used to make up the vesicles, 10:9.5:0.5, cholesterol:PC:MPB-PE, for a total of 20 μmol of lipid (*see* Martin at page 286, column 2, first full paragraph) and the published molecular weights of the components (386.7, 760.1 and 956.2, g/mol respectively), 20 μmol of vesicles is equivalent to 11.6 mg of lipid as set forth below:

cholesterol 10 μmol = 386.7 g/mol x 10 μmol = 3.9 mg

PC 9.5 μmol = 760.1 g/mol x 9.5 μmol = 7.2 mg

MPB-PE 0.5 μmol = 478.1 g/mol x 0.5 μmol = 0.5 mg

Thus, 20 μmol of vesicles = 11.6 mg of lipid.

Therefore:

1 μmol of vesicles = 0.58 mg; and

2 μmol of vesicles = 1.16 mg.

Therefore, the lower and upper bounds of Martin's w/w ratio range of Fab' fragments to vesicles of 0.5-4 mg Fab' fragments to 1-2 μmol lipid is equivalent to:

0.5 mg:1 μmol = 0.5 mg:0.58 mg, or 1 : 1.16

4.0 mg:1 μmol = 4.0 mg:0.58 mg, or 1 : 0.145

to

0.5 mg:2 μmol = 0.5 mg/1.16 mg, or 1 : 2.32

4.0 mg:2 μmol = 4.0 mg/1.16 mg, or 1:0.29

Thus, the ratio range disclosed in Martin is significantly outside the w/w ratio range (1:5 to 1:40) recited in present claim 1. Even if the amount of Fab' fragments referred to in Figure 3 of Martin is used (e.g., about 250 μg Fab' fragments/μmol phospholipid), the range is still well outside the range recited in present claim 1:

250 μg Fab' fragments:1 μmol phospholipid = 0.25 mg:0.58mg, or 1:2.32.

Whether one converts the wt:wt ratio of present claim 1 to wt:molar concentrations, or as shown in the preceding discussion, converts the wt:molar concentrations disclosed in Martin to the wt:wt format used in present claim 1, the end result is the same. The ratios disclosed in Martin and the ratios recited in present claim 1 are very different, and the ordinarily skilled artisan would have found no motivation in Martin, or any of the other references, to modify the ratios as would be required to produce the immunoliposomes of present claim 1.

Therefore, contrary to the examiner's assertion, Martin does not provide a motivation to utilize scFv fragments in the preparation of cationic immunoliposomes. Therefore, Applicants respectfully submit that independent claim 73 cannot be rendered obvious by the disclosure of Martin, alone, or in combination with Yu, Wang and Nilsson. Simply because

Martin may disclose the use of Fab' fragments with liposomes, such a disclosure does not make it obvious that one could use scFv.

Furthermore, with regard to present claim 1, Applicants respectfully submit that it would have required a significant amount of experimentation to modify the ratios disclosed in Martin for use with Fab' fragments to successfully allow the ordinarily skilled artisan to utilize scFvs in a similar manner. Martin provide no guidance for such experimentation or modifications.

Applicants respectfully submit that it is only with the value of hindsight gleaned from the present application that one could find that the cited references suggest immunoliposomes comprising scFv antibody fragments. As the Federal Circuit has held numerous times, a hindsight analysis such as that employed by the Examiner in the present case is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."); *In re Fine*, 5 USPQ2d at 1600 ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant's specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed

invention, "must be founded in the prior art, not in the applicant's disclosure."). The Board has also provided the same mandate on this issue:

> it is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious . . . . a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the Examiner's hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness.

Furthermore, even assuming *arguendo*, that the references do provide the requisite suggestion or motivation, the references provide no practical guidance as they do not suggest what ratios could be, or should be, used to form a stable, scFv-liposome complexes with biological activity. As shown above, the ratios set forth in the references are significantly different from the ratios found to be useful by the present inventors and that are set forth in present claim 1. Applicants respectfully submit that the Examiner has pointed to nothing that would have motivated the ordinarily skilled artisan to make the claimed combination. Moreover, it would require an undue amount of experimentation to arrive at the complex and ratios set forth in claim 1 of the present application. Thus, there cannot be a reasonable expectation of success to make such a combination based on the cited references. Hence, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obvious based up the disclosures of Yu, Wang, Nilsson and Martin, alone or in combination.

Reconsideration and withdrawal of the rejection of claims 1-3, 7, 12, 73 and 74, under 35 U.S.C. § 103(a) are therefore respectfully requested.

The Rejection Under 35 U.S.C. § 103(a) Over Papahadjopoulos, In View of Wang, Martin, Xu and Scherman

In the Office Action at pages 5-8, section 8, the Examiner has rejected claims 1-4, 7, 8, 12, 69, 73 and 74 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Papahadjopoulos *et al.*, U.S. Patent Application No. 2004/0209366 (hereinafter "Papahadjopoulos"), in view of Wang, Martin, Xu *et al.*, *Human Gene Therapy 10*:2941-2952 (1999) (hereinafter "Xu") and Scherman *et al.*, U.S. Patent No. 6,200,956 (hereinafter "Scherman"). Applicants respectfully traverse this rejection.

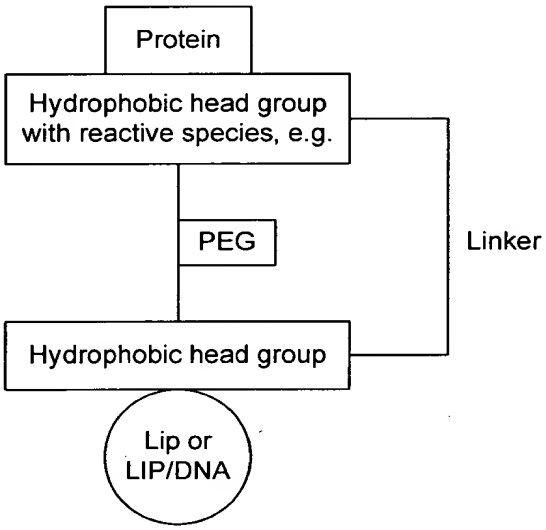
The Examiner contends that Papahadjopoulos discloses the use of a targeting moiety such as antibody fragments, including scFvs, linked to cationic liposomes. The Examiner further contends that Papahadjopoulos discloses that the liposomes can be used to deliver tumor suppressor genes, and that the liposomes may comprise helper lipids DOPE and cholesterol. The Examiner also states the Papahadjopoulos discloses the use of a ratio of antibody:lipid to be 15.6 μg of scFv to 1 μmol lipid, which falls within the w:w range recited in present claim 1.

The Examiner states that Papahadjopoulos does not disclose that the scFvs are bound to DOPE via an MPB linker, nor that that scFvs are capable of binding to a transferrin receptor and that the effector is nucleic acid encoding wild type p53. The Examiner relies on the disclosures of Wang, Martin, Xu and Scherman to cure these deficiencies.

The Examiner contends that Wang discloses generation of an scFv with a carboxy terminal cysteine for the purpose of covalently linking the scFv-cys to a toxin through a disulfide bond. The Examiner further states that Wang discloses the advantages of using scFvs rather than intact antibodies. The Examiner contends that Martin discloses coupling of Fab' fragments to liposomes via a sulfur atom on the Fab' using MPB. The Examiner states that Martin discloses that it is possible to link any thiol-containing protein ligand to MPB-PE containing liposomes. The Examiner also states that Martin discloses coupling Fab' fragments to liposomes at the w/w ratios recited in present claim 1. With regard to Xu, the Examiner states that this reference discloses the use of transferrin-cationic liposomes for delivery of wild type p53 to various tumors. Finally, the Examiner contends that Scherman discloses immunoliposomes comprising transferrin and transferrin antibodies/fragments as targeting molecules for cells such as tumor cells. The Examiner concludes that it would have been obvious for one of ordinary skill in the art to combine these various disclosures to have made the immunoliposomes disclosed in Papahadjopoulos, for delivery of a p53 gene, using a scFv antibody fragment with a specificity for transferrin coupled directly to the liposome via an MPB linkage, based upon the various disclosures of Wang, Martin, Xu and Scherman. Applicants respectfully disagree with the Examiner's conclusion and the contentions on which they are based.

Applicants respectfully submit that Papahadjopoulos does not disclose a nucleic acid-cationic immunoliposome complex in which an scFv antibody fragment is directly conjugated to the liposome as recited in present claim 73, nor a nucleic acid-cationic immunoliposome complex in which an scFv antibody fragment is directly conjugated to the liposome via a sulfur atom which was part of a sulfhydryl group, as recited in present

claim 1. Papahadjopoulos is limited to the use of a linker molecule comprising a hydrophilic domain and hydrophobic domain for attaching antibodies to liposomes. All of the Examples in Papahadjopoulos require the presence of a hydrophilic polymer (PEG) linker (Maleimido-propionylantido-PEG2000-diastearoylphosphatidylethanolamine (Mal-PEG-DSPE)). The linker attaches the scFv either by conjugation or by engineering the linker into the protein. The resultant complex is illustrated below:



Applicants respectfully submit that such complexes clearly are quite different from the complex of present claim 73, in which the scFv is directly conjugated to the liposome. Hence, Papadopoulos is clearly deficient as a primary reference on which to base a *prima facie* case of obviousness with regard to present independent claim 73.

Furthermore, Applicants respectfully submit that Papahadjopoulos does not disclose the 1:5 to 1:40 w/w ratio of protein:lipid recited in present claim 1. Example 5 of Papahadjopoulos provides that the ratio of scFv to lipid was 0.35 mg scFv:150 nmol lipid. This is equivalent to 1 μg scFv:0.489 nmol lipids. This ratio clearly is outside the range of

antibody fragment:lipid of 1 μg:7 nmol to 1 μg:56 nmol scFv:lipid as required in present claim 1 (converted from the w/w ratio range of 1:5 to 1:40; see the discussion of Wang above at pages 10-11 for the conversions of the ratios). In Example 7 of Papahadjopoulos, the ratio of antibody fragment to lipid is 15.6 μg:1 μmol, which also clearly is outside the ratio range required in present claim 1. Hence, Hence, Papadopoulos is clearly deficient as a primary reference on which to base a *prima facie* case of obviousness with regard to present independent claim 1.

Applicants respectfully submit that the deficiencies noted above are not cured by the disclosures of Wang, Martin, Xu and Sherman, alone or in combination. The disclosures of Wang and Martin have been presented above. Wang is limited to conjugation of an scFv to a toxin, not a lipid, and at a ratio well outside the protein to lipid ratio set forth in claim 1. Martin discloses only complexes with Fab' fragments, not scFvs, and provides no disclosure that scFv fragments could be linked to liposomes, much less what ratios of such a fragments to liposome would be useful. As noted above, the ratio of Fab':lipid disclosed Martin is very different from the ratio required in present claim 1, and Martin provides no motivation, much less a reasonable expectation of success, to modify that ratio such that it would fall within the scope of claim 1.

With regard to Xu, Applicants note that the reference does not disclose the use of scFv fragments, disclosing instead complexes in which liposomes are complexed with transferrin, as a targeting ligand. Transferrin and an scFv, such as the transferrin receptor scFv used in examples of the present application, are very different molecules, with different sizes and very different functions. Transferrin is a molecule of about 80 kDa which transports iron; an scFv is an antibody fragment much smaller than transferrin, at about 28

kDa. One of ordinary skill in the art would not expect that one could be substituted for the other, and the Examiner has provided no evidence of any motivation or suggestion of such a substitution.

Scherman does not disclose the use of a ligand of any sort, much less conjugation of scFv fragments to liposomes. The reference does not disclose direct conjugation, including conjugation via a sulfhydryl group, nor what ratios of protein and lipid would be required to prepare the cationic immunoliposomes of the present invention.

As has been explained above, different proteins and different ratios of protein to lipid are not interchangeable. Scherman provides no disclosure of the use of an scFv fragment in a complex with a liposome, nor the direct conjugation of such fragments to a liposome, nor any guidance on the required ratios of antibody fragments to lipids, or nucleic acids to lipids. Thus, Scherman does not cure the deficiencies of the various references noted above.

Furthermore, Applicants respectfully submit that the ordinarily skilled artisan would not have been motivated to combine the disclosures of these references as required by the Examiner. In order to attempt to show the requisite motivation, the Examiner has set forth a series of *eight* steps required to precisely combine selected portions of the various references to produce the presently claimed invention. Applicants respectfully submit that the ordinarily skilled artisan would have found no motivation to combine the portions of the cited references, selectively excerpted by the Examiner, using this complex path required by the Examiner. Indeed, this highly selective approach used by the Examiner, in which portions of the cited references are chosen piecemeal and combined with each other while excluding the remainder of each reference, is the very *epitome* of hindsight reconstruction.

As discussed in detail above, such selective hindsight analysis is impermissible. *See, e.g., Feil*, 774 F.2d at 1143.

Applicants respectfully submit that disclosure of coupling Fab' fragments to liposomes does not lead one of skill in the art to the conclusion that scFvs could also be coupled to liposomes in a similar manner. Therefore, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully submit that claims 1-4, 7, 8, 12, 69, 73 and 74 under 35 U.S.C. § 103(a), are not rendered obvious by the disclosures of Papahadjopoulos, Wang, Martin, Xu and Scherman, alone, or in combination. Hence, reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, rendered moot or otherwise overcome. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and objections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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